



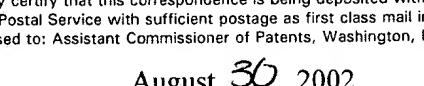
SEP 03 2002

Patent Docket P1735R1

1647  
1889  
R1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

RECEIVED

In re Application of  Ben-Quan Shen et al.  Serial No.: 09/700,806  Filed: November 2, 2000  For: MODULATION OF eNOS ACTIVITY AND THERAPEUTIC USES THEREOF	Group Art Unit: To Be Assigned  Examiner: To Be Assigned	SEP 05 2002  TECH CENTER 1600/2900
<b>CERTIFICATE OF MAILING</b> I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner of Patents, Washington, D.C. 20231 on		
August <u>30</u> , 2002  <u>Emily Dutra</u> Emily Dutra		

## INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner of Patents  
Washington, D.C. 20231

Sir:

Applicants submit herewith patents, publications or other information (attached hereto and listed on the attached revised Form PTO-1449) of which they are aware, which they believe may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 CFR §1.56.

This Information Disclosure Statement is filed in accordance with the provisions of:

[x] 37 CFR §1.97(b)

- within three months of the filing date of the application other than a continued prosecution application under 37 CFR §1.53(d); **or**
- within three months of the date of entry of the national stage of a PCT application as set forth in 37 CFR§1.491, **or**
- before the mailing of the first Office action on the merits; **or**
- before the mailing of the first Office action after the filing of a request for a continued examination under 37 CFR §1.114.

[] 37 CFR §1.97(c)

- by the applicant after the period specified in 37 CFR §1.97(b), but prior to the mailing date of any of a final action under 37 CFR §1.113, or a notice of allowance under 37 CFR §1.311, or an action that otherwise closes prosecution in the application, and is accompanied by either the fee set forth in 37 CFR §1.17(p) or a statement as specified in 37 CFR §1.97(e), as checked below.

[ ] 37 CFR §1.97(d)

- after the period specified in CFR §1.97(c), and is accompanied by the fee set forth in 37

Serial No.: 09/700,806  
Filed: November 2, 2000

Page 2

CFR §1.17(p) and a statement as specified in 37 CFR §1.97(e), as checked below.

[If either of boxes 37 CFR §1.97(c) or 37 CFR §1.97(d) is checked above, the following statement under 37 CFR §1.97(e) may need to be completed.]

- 37 CFR §1.97(e)** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this information disclosure statement.
- 37 CFR §1.704(d)** Each item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application and the communication was not received by any individual designated in §1.56(c) more than thirty days prior to the filing of this information disclosure statement. Therefore, in accordance with the provisions of 37 CFR §1.704(d), the filing of this information disclosure statement will not be considered a failure to engage in reasonable efforts to conclude prosecution under 37 CFR §1.704.
- The U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of \$180.00 to cover the cost of this Information Disclosure Statement under 37 CFR §1.17(p). Any deficiency or overpayment should be charged or credited to this deposit account.

A list of the patent(s) or publication(s) is set forth on the attached revised Form PTO-1449 (Modified).

**A copy of the items on PTO-1449 is supplied herewith.**

Those patent(s) or publication(s) which are marked with an asterisk (\*) in the attached PTO-1449 form are not supplied because they were previously cited by or submitted to the Office in a prior application Serial No. 60/163,132, filed November 2, 1999 and relied upon in this application for an earlier filing date under 35 USC §120.

- BLAST results enclosed:

The undersigned also wishes to bring to the attention of the Examiner BLAST results of computerized alignments of the against sequences contained in the nucleotide and protein databases. The BLAST results are provided in paper form and are identified as reference "BLAST Results A-1- A-()" (nucleotide) and "BLAST Results B-1 - B-()" (protein) on the PTO Form 1449. Applicant requests that these references also be considered and that the Form 1449 be initialed to indicate the Examiner's consideration of the references.

A concise explanation of relevance of the items listed on PTO-1449 is:

- not given
- given for each listed item

Serial No.: 09/700,806  
Filed: November 2, 2000

Page 3

given for only non-English language listed item(s) [Required]  
An English language abstract is included with item 12 of the FORM PTO-1449.

in the form of an English language copy of a Search Report from a foreign patent office, issued in a counterpart application, which refers to the relevant portions of the references.

In accordance with 37 CFR §1.97(g), the filing of this information disclosure statement shall not be construed as a representation that a search has been made.

In accordance with 37 CFR §1.97(h), the filing of this information disclosure statement shall not be construed to be an admission that the information cited in the statement is, or is considered to be, material to patentability as defined in 37 CFR § 1.56(b).

In the event that the Office determines a fee to be due where none is specifically authorized in this paper, the U.S. Patent and Trademark Office is hereby authorized to charge Deposit Account No. 07-0630 in the amount of \$180.00 to cover the cost of this Information Disclosure Statement under 37 CFR §1.17(p).

Respectfully submitted,

GENENTECH, INC.

By: Steven X. Cui  
Steven X. Cui  
Reg. No. 44,637  
Telephone No. (650) 225-8674



09157

PATENT TRADEMARK OFFICE

FORM PTO-1449		U.S. Dept. of Commerce Patent and Trademark Office		Atty Docket No. P1735R1	Serial No. 09/700,806
LIST OF DISCLOSURES CITED BY APPLICANT (Use several sheets if necessary)				Applicant Ben-Quan Shen et al.	
				Filing Date 02 Nov 2000	Group

## U.S. PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Name	Class	Subclass	Filing Date
	1	3,773,919	20.11.73	Boswell, G.			RECEIVED
	2	3,887,699	03.06.75	Yolles, S.			SEP 05 2002
	3	4,816,567	28.03.89	Cabilly et al.			
	4	5,545,806	13.08.96	Lonberg et al.			
	5	5,545,807	13.08.96	Surani et al.			
	6	5,569,825	29.10.96	Lonberg et al.			
	7	5,625,126	29.04.97	Lonberg et al.			
	8	5,633,425	27.05.97	Lonberg et al.			
	9	5,661,016	26.08.97	Lonberg et al.			

## FOREIGN PATENT DOCUMENTS

Examiner Initials		Document Number	Date	Country	Class	Subclass	Translation Yes	Translation No
	10	1,176,565	23.10.84	CANADA				
	11	058,481	25.08.82	EPO				
	12	158,277	16.10.85	EPO (ENGLISH ABSTRACT ATTACHED)				
	13	WO 90/13649	15.11.90	PCT				

## OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

14	Boerner et al., "Production of Antigen-Specific Human Monoclonal Antibodies From In Vitro-Primed Human Splenocytes" <u>The Journal of Immunology</u> 147(1):86-95 (1991)
15	Burgess and Maciag, "The Heparin-Binding (Fibroblast) Growth Factor Family of Proteins" <u>Annu. Rev. Biochem.</u> 58:575-606 (1989)
16	Busse and Fleming., "Endothelial Dysfunction in Atherosclerosis." <u>J. Vasc. Res.</u> 33:181-194 (1996)
17	Cao, Yihai et al., "Heterodimers of Placenta Growth Factor/Vascular Endothelial Growth Factor." <u>J. Bio. Chem.</u> 271:3154-3162 (1996)
18	De Vries et al., "The fms-Like Tyrosine Kinase, A Receptor for Vascular Endothelial Growth Factor." <u>Science</u> . 255:989-991 (Feb 1992)
19	Drummond and Harrison., "eNOS-Overexpressing Mice: Too Much NO Makes the Blood Pressure Low." <u>J. Clin. Invest.</u> 102:2033-2034 (Dec 1998)
20	Ferrara and Davis-Smyth., "The Biology of Vascular Endothelial Growth Factor." <u>Endocrine Reviews</u> . 18(1):4-25 (1997)
21	Ferrara and Henzel, "Pituitary Follicular Cells Secrete a Novel Heparin-binding Growth Factor Specific for Vascular Endothelial Cells" <u>Biochem. &amp; Biophys. Res. Comm.</u> 161(2):851-858 (1989)
22	Fishwild et al., "High-Avidity Human IgG <sub>1</sub> Monoclonal Antibodies From a Novel Strain of Minilocus Transgenic Mice" <u>Nature Biotechnology</u> . 14(7):845-851 (Jul 1996)
23	Folkman., "Angiogenesis in Cancer, Vascular, Rheumatoid and Other Disease." <u>Nature Medicine</u> . 1(1):27-31 (1995)

Examiner	Date Considered
----------	-----------------

\*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

FORM PTO-1449

SEP 03 2002

FILING &amp; TRADEMARK RECEIVING

U.S. Dept. of Commerce  
Patent and Trademark OfficeAtty Docket No.  
P1735R1Serial No.  
09/700,806

Applicant

Ben-Quan Shen et al.

Filing Date

02 Nov 2000

RECEIVED  
SEP 05 2002

## LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

TECH CENTER 1600/2901

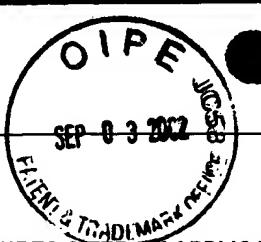
## OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

24	Fuh et al., "Requirements for Binding and Signaling of the Kinase Domain Receptor for Vascular Endothelial Growth Factor." <u>J. Bio. Chem.</u> 273(18):11197-11204 (May 1, 1998)
25	Hariawala et al., "VEGF Improves Myocardial Blood Flow but Produces EDRF-Mediated Hypotension in Porcine Hearts." <u>J. Surg. Res.</u> 63:77-82 (1996)
26	Hood et al., "VEGF Upregulates ecNOS Message, Protein, and NO Production in Human Endothelial Cells." <u>Am. J. Phys.</u> 274:H1054-H1058 (1998)
27	Hoogenboom and Winter, "By-Passing Immunisation: Human Antibodies from Synthetic Repertoires of Germline VH Gene Segments Rearranged in Vitro" <u>J. Mol. Biol.</u> 227:381-388 (1992)
28	Houck et al., "The Vascular Endothelial Growth Factor Family: Identification of a Fourth Molecular Species and Characterization of Alternative Splicing of RNA." <u>Mol. Endocrinol.</u> 5:1806-1814 (1991)
29	Ishikawa et al., "Identification of Angiogenic Activity and the Cloning and Expression of Platelet-Derived Endothelial Cell Growth Factor." <u>Nature</u> . 338:557-562 (1989)
30	Jin et al., "Novel Analog of Atrial Natriuretic Peptide Selective for Receptor-A Produces Increased Diuresis and Natriuresis in Rats." <u>J. Clinical Investigation</u> . 98(4):969-976 (Aug 15, 1996)
31	Jones et al., "Replacing the Complementarity-Determining Regions in a Human Antibody with those from a Mouse" <u>Nature</u> 321:522-525 (May 29, 1986)
32	Keyt et al., "Identification of Vascular Endothelial Growth Factor Determinants for Binding KDR and FLT-1 Receptors: Generation of Receptor-Selective VEGF Variants by Site-Directed Mutagenesis." <u>Journal of Biological Chemistry</u> 271(10):5638-5646 (1996)
33	Keyt et al., "The Carboxyl-terminal Domain (111-165) of Vascular Endothelial Growth Factor Is Critical for Its Mitogenic Potency" <u>Journal of Biological Chemistry</u> 271(13):7788-7795 (Mar 29, 1996)
34	Kroll et al., "VEGF-A Induces Expression of eNOS and iNOS in Endothelial Cells via VEGF Receptor-2 (KDR)." <u>Biochem. &amp; Biophys. Res. Comm.</u> 252:743-746 (1998)
35	Langer., "Controlled Release of Macromolecules." <u>Chemtech</u> . 12:98-105 (Feb 1982)
36	Leung et al., "Vascular Endothelial Growth Factor is a Secreted Angiogenic Mitogen" <u>Science</u> 246:1306-1309 (1989)
37	Liu et al., "Angiogenesis Activators and Inhibitors Differentially Regulate Caveolin-1 Expression and Caveolae Formation in Vascular Endothelial Cells." <u>J. Bio. Chem.</u> 274:15781-15785 (1999)
38	Lonberg and Huszar., "Human Antibodies From Transgenic Mice" <u>International Reviews of Immunology</u> 13(1):65-93 (1995)
39	Lonberg et al., "Antigen-Specific Human Antibodies From Mice Comprising Four Distinct Genetic Modifications" <u>Nature</u> . 368(6474):856-859 (Apr 28, 1994)
40	Luscher., "Endogenous and Exogenous Nitrates and Their Role in Myocardial Ischaemia." <u>Br. J. Clin. Pharmacol.</u> (Suppl. 1) 34:29S-35S (1992)
41	Malavaud et al., "Activation of Flk-1/KDR Mediates Angiogenesis but not Hypotension." <u>Cardiovascular Research</u> . 36(2):276-281 (Nov 1997)
42	Marks et al., "By-Passing Immunization: Building High Affinity Human Antibodies by Chain Shuffling" <u>Bio/Technology</u> 10:779-783 (1992)
43	Marks et al., "By-Passing Immunization: Human Antibodies From V-gene Libraries Displayed On Phage" <u>J. Mol. Biol.</u> 222:581-597 (1991)

Examiner

Date Considered

\*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



FORM PTO-1449

U.S. Dept. of Commerce  
Patent and Trademark Office

Atty Docket No.

P1735R1

Serial No.

09/100/2000

Applicant

Ben-Quan Shen et al.

Filing Date

02 Nov 2000

SEP 05 2002

Group

## LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

RECEIVED  
TECH CENTER 1600/2900C

## OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

44	Matthews et al., "A Receptor Tyrosine Kinase cDNA Isolated from a Population of Enriched Primitive Hematopoietic Cells and Exhibiting Close Genetic Linkage to c-kit." <u>Proc. Natl. Acad. Sci.</u> 88:9026-9030 (1991)
45	Meyer et al., "A Novel Vascular Endothelial Growth Factor Encoded by Orf Virus, VEGF-E, Mediates Angiogenesis Via Signalling Through VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) Receptor Tyrosine Kinases." <u>EMBO Journal</u> 18(2):363-374 (Jan 15, 1999)
46	Migdal et al., "Neuropilin-1 is a Placenta Growth Factor-2 Receptor." <u>J. Bio. Chem.</u> 273:22272-22278 (Aug 1998)
47	Morbidelli et al., "Nitric Oxide Mediates Mitogenic Effect of VEGF on Coronary Venular Endothelium." <u>Am. J. Physiol.</u> 270:H411-H415 (1996)
48	Morrison et al., "Chimeric Human Antibody Molecules: Mouse Antigen-Binding Domains with Human Constant Region Domains" <u>Proc. Natl. Acad. Sci. USA</u> 81:6851-6855 (November 1984)
49	Morrison, S., "Immunology: Success in Specification" <u>Nature</u> 368(6474):812-813 (Apr 28, 1994)
50	Muller et al., "The Crystal Structure of Vascular Endothelial Growth Factor (VEGF) Refined to 1.93 Å Resolution: Multiple Copy Flexibility and Receptor Binding." <u>Structure</u> 5(10):1325-1338 (Oct 15, 1997)
51	Muller et al., "Vascular Endothelial Growth Factor: Crystal Structure and Functional Mapping of the Kinase Domain Receptor Binding Site." <u>Proc. Natl. Acad. Sci. USA</u> 94(14):7192-7197 (Jul 8, 1997)
52	Murohara et al., "Nitric Oxide Synthase Modulates Angiogenesis in Response to Tissue Ischemia." <u>J. Clin. Invest.</u> 101:2567-2578 (Jun 1998)
53	Nathan and Xie., "Regulation of Biosynthesis of Nitric Oxide." <u>J. Bio. Chem.</u> 269:13725-13728 (May 1994)
54	Neuberger, M., "Generating High-Avidity Human Mabs in Mice" <u>Nature Biotechnology</u> . 14(7):826 (Jul 1996)
55	Ogawa et al., "A Novel Type of Vascular Endothelial Growth Factor, VEGF-E (NZ-7 VEGF), Preferentially Utilizes KDR/Flk-1 Receptor and Carries a Potent Mitotic Activity Without Heparin-Binding Domain." <u>J. Bio. Chem.</u> 273(47):31273-31282 (Nov 20, 1998)
56	Ohashi et al., "Hypotension and Reduced Nitric Oxide-Elicited Vasorelaxation in Transgenic Mice Overexpressing Endothelial Nitric Oxide Synthase." <u>J. Clin. Invest.</u> 102:2061-2071 (Dec 1998)
57	Olofsson et al., "Vascular Endothelial Growth Factor B (VEGF-B) Binds to VEGF Receptor-1 and Regulates Plasminogen Activator Activity in Endothelial Cells." <u>Proc. Natl. Acad. Sci. USA</u> 95(20):11709-11714 (Sep 29, 1998)
58	Papapetropoulos et al., "Nitric Oxide Production Contributes to the Angiogenic Properties of Vascular Endothelial Growth Factor in Human Endothelial Cells." <u>J. Clin. Invest.</u> 100:3131-3139 (Dec 1997)
59	Parenti et al., "Nitric Oxide is an Upstream Signal of Vascular Endothelial Growth Factor-Induced Extracellular Signal-Regulated Kinase1/2 Activation in Postcapillary Endothelium." <u>J. Bio. Chem.</u> 273:4220-4226 (Feb 1998)
60	Pepper., "Manipulating Angiogenesis: From Basic Science to the Bedside." <u>Arterioscler. Thromb. Vasc. Bio.</u> 17:605-619 (1997)
61	Presta, L., "Antibody Engineering" <u>Curr. Op. Struct. Biol.</u> 2:593-596 (1992)
62	Riechmann et al., "Reshaping Human Antibodies for Therapy" <u>Nature</u> 332:323-327 (Mar 24, 1988)
63	Rudic et al., "Direct Evidence for the Importance of Endothelium-Derived Nitric Oxide in Vascular Remodeling." <u>J. Clin. Invest.</u> 101:731-736 (Feb 1998)

Examiner

Date Considered

\*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

O I P E  
SEP 03 2002

FORM PTO-1449

U.S. Dept. of Commerce  
Patent and Trademark Office

Atty Docket No.

P1735R1

Serial No.

09/700,606

Applicant

Ben-Quan Shen et al.

Filing Date

02 Nov 2000

SEP 05 2002

LIST OF DISCLOSURES CITED BY APPLICANT

(Use several sheets if necessary)

RECEIVED  
TECH CENTER 1600/290

## OTHER DISCLOSURES (Including Author, Title, Date, Pertinent Pages, etc.)

64	Sase and Michel., "Expression and Regulation of Endothelial Nitric Oxide Synthase." <u>Trends Cardiovasc. Med.</u> 7:28-37 (1997)
65	Shen et al., "Hepatocyte Growth Factor Stimulates the Differentiation of Human Tracheal Epithelia In Vitro." <u>Am. J. Physiol.</u> 272:L1115-L1120 (1997)
66	Shen et al., "Homologous Up-Regulation of KDR/Flk-1 Receptor Expression by Vascular Endothelial Growth Factor In Vitro." <u>J. Bio. Chem.</u> 273:29979-29985 (Nov 1998)
67	Shibuya et al., "Nucleotide Sequence and Expression of a Novel Human Receptor-Type Tyrosine Kinase Gene (flt) Closely Related to the fms Family." <u>Oncogene</u> 5:519-524 (1990)
68	Sidman et al., "Controlled Release of Macromolecules and Pharmaceuticals from Synthetic Polypeptides Based on Glutamic Acid" <u>Biopolymers</u> 22(1):547-556 (1983)
69	Siemeister et al., "Expression of Biologically Active Isoforms of the Tumor Angiogenesis Factor VEGF in Escherichia coli." <u>Biochem. &amp; Biophys. Res. Comm.</u> 222:249-255 (1996)
70	Soker et al., "Neuropilin-1 is Expressed by Endothelial and Tumor Cells as an Isoform-Specific Receptor for Vascular Endothelial Growth Factor." <u>Cell.</u> 92:735-745 (Mar 1998)
71	Terman et al., "Identification of a New Endothelial Cell Growth Factor Receptor Tyrosine Kinase." <u>Oncogene</u> 6:1677-1683 (1991)
72	Terman et al., "Identification of the KDR Tyrosine Kinase as a Receptor for Vascular Endothelial Cell Growth Factor." <u>Biochem. &amp; Biophys. Res. Comm.</u> 187:1579-1586 (1992)
73	Tischer et al., "Vascular Endothelial Growth Factor: A New Member of the Platelet-Derived Growth Factor Gene Family." <u>Biochem. &amp; Biophys. Res. Comm.</u> 165:1198-1206 (1989)
74	van der Zee et al., "Vascular Endothelial Growth Factor/Vascular Permeability Factor Augments Nitric Oxide Release From Quiescent Rabbit and Human Vascular Endothelium." <u>Circulation</u> . 95:1030-1037 (1997)
75	Verhoeven, M. et al., "Reshaping Human Antibodies: Grafting an Antilysozyme Activity" <u>Science</u> 239:1534-1536 (Mar 25, 1988)
76	Waltenberger et al., "Different Signal Transduction Properties of KDR and Flt1, Two Receptors for Vascular Endothelial Growth Factor." <u>J. Bio. Chem.</u> 269(43):26988-26995 (Oct 28, 1994)
77	Wiesmann et al., "Crystal Structure at 1.7 Å Resolution of VEGF in Complex with Domain 2 of the Flt-1 Receptor." <u>Cell.</u> 91:695-704 (Nov 1997)
78	Wu et al., "VEGF Induces NO-Dependent Hyperpermeability in Coronary Venules." <u>Am. J. Physiol.</u> 271:H2735-H2739 (1996)
79	Yang et al., "Effects of Vascular Endothelial Growth Factor on Hemodynamics and Cardiac Performance." <u>J. Cardiovasc. Pharmacol.</u> 27:838-844 (1996)
80	Ziche et al., "Nitric Oxide Synthase Lies Downstream from Vascular Endothelial Growth Factor-Induced but not Basic Fibroblast Growth Factor-Induced Angiogenesis." <u>J. Clin. Invest.</u> 99:2625-2634 (Jun 1997)

Examiner

Date Considered

\*Examiner: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.